A Practical Preparation of Terminal Alkynes from Aldehydes

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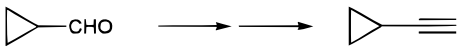
As a part of the project for the development of an economical and efficient synthesis of Efavirenz (Sustiva, DMP 266), a marketed nonnucleoside reverse transcriptase inhibitor of the HIV-1 virus developed by our company for the treatment of AIDS,[1] we have searched for new methodologies for the synthesis of cyclopropylacetylene **1** (CPA). As discussed previously,[2] we anticipated that the most efficient synthesis of **1** would occur from cyclopropylcarboxaldehyde via a one carbon homologation.



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Alkynes are useful and versatile intermediates in organic synthesis.[3] The utility of the acetylenic functional group in organic chemistry has been well documented.[4] The most frequently used methods for the conversion of aldehydes to terminal alkynes include the reactions of Corey−Fuchs,[5] Wittig/Horner−Emmons,[6] and Gilbert−Seyferth[7] and its modifications.[8] However, the need for phosphorus reagents limits the usefulness of these applications due to toxicity, exothermicity, and voluminous waste streams, particularly for large scale preparations. As an extension of our preparation of **1**, we have developed an alternative approach for the conversion of aldehydes to terminal alkynes through a three-step reaction sequence: addition of dihalomethyllithium to aldehydes, sulfonation of the adducts, and then elimination of chloride and tosylate followed by elimination of HX to generate the desired alkynes.[2] Although this is a good method for the synthesis of alkynes from aldehydes, it is still necessary to handle a thermolabile and moisture-sensitive species, dihalomethyllithium, at low temperature (−78 to −50 °C) for good yields. To better meet our project needs, we have developed a better preparation of **1** and a general reaction sequence for the conversion of aldehydes to terminal alkynes. In this report, we disclose a new methodology for the synthesis of terminal alkynes. This process has three steps: (1) addition of trichloromethyl anion generated in situ from trichloroacetic acid to aldehydes **2** to form trichloro alcohols **3**; (2) transformation of **3** into trichlorosulfonates **4**; and finally, (3) sequential elimination of chloride, tosylate, and HCl followed by metalation of the remaining chloride and protonation to generate the desired alkynes, **5** (Scheme 1).

This procedure works well for our target: cyclopropylacetylene **1**. We have applied this procedure for the synthesis of cyclopropylacetylene in 300−400 g scale in approximately 80% overall yield. Furthermore, this reaction sequence provides a simple, reliable, and economical general methodology for the conversion of aldehydes to terminal alkynes with excellent yields (Table 1).

Trichlorocarbinols are useful synthons in organic synthesis,[9] which can be obtained by the reaction of chloroform and strong base in the presence of an aldehyde.[10] Recently, the Corey group developed a superior method for the preparation of trichlorocarbinols which we found fits well into our reaction sequence.[11] In the presence of aldehydes, trichloromethyl anion was generated by decarboxylation at room temperature when trichloroacetic acid was mixed with sodium trichloroacetate in DMF, which in turn added to aldehydes **2** to form the desired trichloromethyl carbinols **3**. The release of carbon dioxide of this reaction was observed during the first 5−10 min after the addition of sodium trichloroacetate in one portion; however, it took 1.5−2.0 h for the completion of the decarboxylation. The yields of the preparation of trichlorocarbinols are summarized in Table 1.

The trichlorocarbinols **3** were efficiently transformed into their corresponding acetate or methanesulfonate esters by treatment with acetyl chloride or methanesulfonyl chloride, respectively, in the presence of triethylamine. However, some of these compounds were low-melting solids, inconvenient for large-scale purification. Instead, we turned our attention to synthesize trichlorocarbinol *p*-toluenesulfonates **4**. The conventional methods[12] (*p*-toluenesulfonyl chloride, triethylamine or pyridine) for the synthesis of tosylates **4** produced poor results, probably due to the steric hindrance arising from three chlorine atoms adjacent to the hydroxide in the molecules **3**. It is possible to convert cyclopropyl trichlo-

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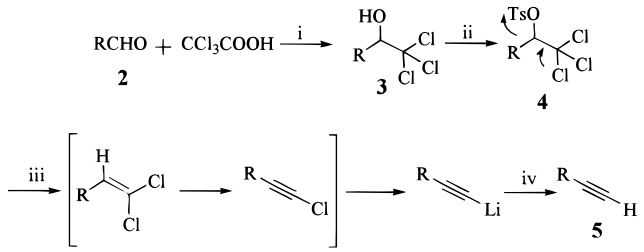
Scheme 1. General Method for 1-Alkyne Preparation[a]



[a] Reagents: (i) CCl_3COONa, 1.5 equiv/DMF, 25−35 °C; (ii) TsCl/TEA/DABCO, cat./CH_2Cl_2, 25 °C; (iii) 4.5 eq MeLi/THF, −10 °C; (iv) H_3O^+.

Table 1. Summary of the Yields of Trichlorocarbinols 3, Alkylsulfonates 4, and Acetylenes 5

entry	R−CHO	**3a−g**, % yield	**4a−g**, % yield[a]	**5a−g**, % yield
a	cyclopropyl	95	91	94[b]
b	cyclohexyl	94	78	87
c	isobutyl	88	89	90[b]
d	*n*-octyl	85	90	95
e	*tert*-butyl	89	68[c]	81[b]
f	phenyl	90	75	89
g	2-phenylethyl	90	82	98
h	cyclopropyl	*d*	92[c]	95[b]

[a] Yield of pure compound after recrystallization based on the trichlorocarbinols unless otherwise stated. [b] Product isolated as THF/ether/hexane solution; yield determined by GC. [c] Mesylate was produced instead of tosylate. [d] Not isolated.

rocarbinol into the corresponding tosylate by treatment with toluenesulfonic anhydride in the presence of triethylamine in 90% yield. However, we did not pursue this reaction further due to poor atomic efficiency. To our delight, we found that the addition of a catalytic amount of DABCO under the initially explored conditions (*p*-toluenesulfonyl chloride, triethylamine) produced a good to excellent yield of **4**. Remarkably, only DABCO out of a series bases is effective for this reaction; even the closely related bases, i.e., DBN and DBU, failed. Using these reaction conditions, all the trichlorocarbinols **3** were converted to their corresponding tosylate derivatives (except *tert*-butyl trichlorocarbinol **3e**, which was too hindered). The trichlorosulfonates are crystalline compounds, and the purification was possible by recrystallization from ethyl acetate:heptane, when necessary.

The trichlorosulfonates were transformed into their corresponding terminal alkynes through elimination with strong bases, such as methyllithium or sodamide/DMSO. The elimination proceeded via a stepwise mechanism. Initially, one chloride was metalated to form a carbenoid species: $RCH(OTS)-C(Li)Cl_2$, which lost tosylate to form a vinyl dichloride intermediate ($RCH{=}CCl_2$). This underwent further elimination of hydrogen chloride to generate a chloroacetylene, which in turn was metalated under reductive conditions to form the acetylide salt. The desired acetylenes were obtained after aqueous workup and were either isolated by distillation or as concentrated solution. Revealingly, when a trichloro sulfonate, such as **4a**, was treated with 1 equiv of methyllithium or sodamide/DMSO, three species, the vinyl dichloride ($C_3H_5CHC{=}CCl_2$), chloroacetylene ($C_3H_5C{\equiv}CCl$), and the desired acetylene ($C_3H_5C{\equiv}CH$) were observed by GC and proton NMR spectroscopy. Thisobservation supports the mechanism described in Scheme 1.

In summary, we have developed an efficient, practical, and economical procedure for the conversion of aldehydes into terminal alkynes. Of particular importance to us is a practical and commercially viable preparation of cyclopropylacetylene, a key component of Sustiva.

Experimental Section

General. All NMR spectra recorded in $CDCl_3$. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. GC analyses was conducted using a J&W DB-1 column (i.d. 0.32 mm × 30 m). Oils were purified by flash chromatography,[10] typically by ethyl acetate/heptane on silica gel. Crude yields are reported unless stated otherwise. Combustion analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ.

Preparation of Trichlorocarbinols (3a−g). The following procedure for cyclopropyl trichlorocarbinol **3a** is representative:

α-(Trichloromethyl)cyclopropanemethanol (3a). To a stirred solution of trichloroacetic acid (960.7 g, 5.88 mol) and cyclopropylcarboxaldehyde (275.0 g, 3.92 mol) in DMF (2.5 L) at 25 °C was added sodium trichloroacetate (1090 g, 5.88 mol) portionwise so as to maintain temperature below 35 °C. After the addition was complete, the mixture was stirred at 25 °C for 4 h. The reaction was monitored by ^1H NMR spectroscopy using the disappearance of the aldehyde proton signal as an end point. After reaction was complete, the solution was cooled to 5 °C and quenched with water. The heterogeneous emulsion was diluted with water and extracted with hexane. The combined organic solutions were washed with water and saturated ammonium chloride. The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum to produce 699.0 g (94%) of α-(trichloromethyl)cyclopropanemethanol as a dark oil. No further purification was needed: bp 45°−47 °C/8 Torr. TLC: $R_f = 0.55$ hexane/ethyl acetate, (4:1, v/v). ^1H NMR ($CDCl_3$) δ: 0.62−0.73 (m, 2H), 0.75−0.84 (m, 2H), 1.20−1.38 (m, 1H), 3.60 (d, 1H, J = 10.0 Hz). ^{13}C NMR δ: 2.02, 5.80, 13.0, 85.82, 104.0.

α-(Trichloromethyl)cyclohexanemethanol (3b): oil, yield: 94%.

1,1,1-Trichloro-4-methyl-2-pentanol (3c): oil, yield: 88%.

1,1,1-Trichloro-2-decanol (3d): oil; yield: 85%.

1,1,1-Trichloro-3,3-dimethyl-2-butanol (3e): oil, yield: 89%.

α-(Trichloromethyl)benzenemethanol (3f): oil, yield: 90%.

α-(Trichloromethyl)benzenepropanol (3g): oil, yield: 89%.

Preparation of Trichloro Tosylates (4a−d,f,g). The following procedure for cyclopropyl trichlorocarbinol **4a** is representative:

α-(Trichloromethyl)cyclopropanemethanol 4-Methylbenzenesulfonate (4a). To a stirred solution of **3a** (40.0 g, 0.211 mol), triethylamine (32.1 g, 0.317 mol), and DABCO (7.1 g, 0.063 mol) in methylene chloride (400 mL) at 25 °C was added *p*-toluenesulfonyl chloride (40.2 g, 0.211 mol). The solution was stirred for 1.5 h at 25 °C and quenched with water. The organic phase was successively washed with 5 M HCl and water. The combined aqueous phases were extracted with methylene chloride. The organic extracts were combined and washed with 2 N HCl, water, and brine. The solution was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by recrystallization (4:1 mixture hexane/ethyl acetate) to produce 66.1 g (91%) of **4a**: mp 74−75 °C. ^1H NMR δ ($CDCl_3$): 0.62−0.95 (m, 4H), 1.40−1.52 (m, 1H), 2.45 (s, 3H), 4.60 (d, J = 11.4 Hz, 1H), 7.32 (d, J = 9.9 Hz, 2H), 7.82 (d, J = 9.90 Hz, 2H). ^{13}C NMR δ: 3.09, 7.82, 12.90, 21.85, 92.15, 99.02, 126.8, 127.0 129.9, 130.0, 134.5, 145.0. Anal. Calcd for $C_{12}H_{13}Cl_3O_3S$: C, 41.94; H, 3.81; S 9.33. Found: C, 41.97; H, 3.77; S, 9.33.

α-(Trichloromethyl)cyclohexanemethanol 4-methylbenzenesulfonate (4b): white crystals, yield: 78%. mp: 117.5−118 °C.

1,1,1-Trichloro-4-methyl-2-pentanol 4-methylbenzenesulfonate (4c): white crystals, yield: 89%. mp: 118−120 °C.

1,1,1-Trichloro-2-decanol 4-methylbenzenesulfonate (4d): oil, yield: 90%.

1,1,1-(Trichloromethyl)benzenemethanol 4-methylbenzenesulfonate (4f): white crystals, yield: 75%. mp: 126.3−127.6 °C.

α-(Trichloromethyl)benzenepropanol methylbenzenesulfonate (4g): white crystals, yield: 82%. mp: 85.3−86.2 °C.

Preparation of Trichloromesylates (4e and 4h). The following procedure for cyclopropyl mesylate **4h** is representative:

α-(Trichloromethyl)cyclopropanemethanol Methanesulfonate (4h). To a stirred solution of **3a** (250 g, 1.319 mol), triethylamine (276 mL, 1.979 mol, 1.5 equiv), and DABCO (44.4 g, 0.396 mol) in methylene chloride (1000 mL) at 0 °C was added methanesulfonyl chloride (112.3 mL, 1.451 mol). The solution was warmed to 25 °C, stirred for 1.5 h, and quenched with water. The organic phase was successively washed with 5 M HCl and water. The combined aqueous phases were extracted with CH_2Cl_2. The organic extracts were combined and sequentially washed with an aqueous solution of 2 N NaOH, water, and brine. This solution was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by recrystallization (4:1 mixture hexane/ethyl acetate) to produce 324.7 g (92%) of **4h** as white crystals: mp 46.3−48.6 °C. ^{1}H NMR ($CDCl_3$) δ: 0.78−0.92 (m, 3H), 0.97−1.02 (m, 1H), 1.50 (m, 1H), 3.20 (s, 3H), 4.50 (d, J = 11.4 Hz, 1H). ^{13}C NMR δ: 3.88, 7.80, 12.74, 39.90, 92.05, 98.02. Anal. Calcd for $C_6H_9Cl_3O_3S$: C, 26.94; H, 3.39; S, 11.99. Found: C, 26.94; H, 3.42; S, 12.03.

1,1,1-Trichloro-3,3-dimethyl-2-butanol methanesulfonate (4e): white crystals, yield: 68%. mp: 61.5−63 °C.

Preparation of Acetylenes 5a−g. The following procedure for cyclopropylacetylene **5a** is representative for the conversion of both trichloro tosylates and trichloro mesylates using methyllithium.

Ethynylcyclopropane (5a). To a stirred solution of **4a** (17.2 g, 50.0 mmol) in THF (300 mL) at −10 °C was added methyllithium (161.0 mL of 1.4 M solution in ether, 225.0 mmol) dropwise. The solution was warmed to 0 °C over 1 h. The reaction was quenched with saturated ammonium chloride and diluted with hexane, and the layers were separated. (If the product was not hexane soluble, methyl *tert*-butyl ether was used instead throughout this experiment). The aqueous phase was extracted with hexane (3 × 100 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$ and filtered. This produced a solution of 3.16 g of **5a** within 740 g of THF/ether/hexane solution (94.5% solution yield). Distillation afforded 3.05 g (93%, 99.3 GC area %) of neat **5a**: bp 53−55 °C. ^{1}H NMR δ: 1.75 (d, J = 6.1 Hz, 1H), 1.24 (m, 1H), 0.78 (m, 2H), 0.72 (m, 2H). ^{13}C NMR δ: 87.6, 63.3, 8.0, −0.88.

Acetylenes of higher boiling point were stripped of most of their solvents, and the purity was either measured by GC versus dilutions of the known standard or stated as GC area %. Acetylenes that were distilled are listed as such. All acetylenes are known compounds.

Ethynylcyclohexane[14] **(5b):** oil; yield: 87%; 98.2 GC area %.

4-Methylpentyne[15] **(5c):** oil; yield: 90%; 94.0 wgt %.

***n*-Octyne**[16] **(5d):** oil (distilled); yield: 95%; 98.0 GC area %.

3,3-Dimethyl-1-butyne[17] **(5e):** oil; yield: 81%; 84.0 wgt %.

Ethynylbenzene[18] **(5f):** oil (distilled); yield: 89%; 98.7 GC area %.

3-Butynylbenzene[19] **(5g):** oil; yield: 98%; 98.8 GC area %.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **4d**. The characterization data for analogue compounds **3b−g**, **4b−g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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